Docket No.: 57721-20001.01
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christopher J. STANLEY

Confirmation No.: 5588

Application No.: 09/760,819

Art Unit: 1634

Filed: January 17, 2001

Examiner: F. Lu

For: USE OF NUCLEIC ACIDS BOUND TO CARRIER MACROMOLECULES

DECLARATION OF SAMUEL A. LEWIS, Ph.D. UNDER 37 CFR § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

[0001] I am employed as a Scientist with AZURE Institute, at 4108 Sorrento Valley Blvd., San Diego, California (AZURE Institute is affiliated with Oakville Hong Kong Co., Ltd., which is the assignee of the captioned patent application). I graduated from Johns Hopkins, School of Medicine with a Ph.D. in Pharmacology in 1987. I have 19 years of experience working in biomedical research/development and manufacturing of biological materials. I have cultured over 70 pathogens and developed laboratory or commercial diagnostic tests for most of the pathogens. In 1988, I was the first person to setup and use PCR on Plum Island, New York, which is the U.S. Dept. of Agriculture's research center for exotic diseases affecting animals. In 2001, I was the head of the Molecular Diagnostic section of the Virology Program at the U.S. Navy's Medical Research Center in Cairo, Egypt. The section developed and used PCR to diagnose exotic diseases. I have published 9 papers in peer-reviewed publications in the area of the molecular biology of infectious disease. Appendix A provides a list of these publications.

EXHIBIT 1

[0002] I have reviewed the specification of the captioned patent application. I have been asked to provide my professional opinion on the meaning of term "polymer" in the context of the specification. I have also been asked to opine on the meaning in the art of the term "carrier macromolecule." I have been informed that the terms should be interpreted according to the ordinary and accustomed meanings of the terms, as would be understood by a person of ordinary skill in the art, which in the present case is nucleic acid assays and amplifications. I am also informed that the terms should be interpreted in the context of the specification of the patent application, as it would be understood by a person of ordinary skill in the art.

[0003] I am informed that in this case the Examiner has taken the position that fluorescein is a "polymer." In the context of the specification of the captioned case, indeed in the context of the field of chemistry, this is neither an ordinary meaning nor an accepted meaning of the term. A polymer is a molecule formed by combining (polymerizing) sub-units, called monomers, in a regular pattern. Examples of polymers are starch (which has many sugar units), polyethylene (which has many ethylene units) and polystyrene (which has many styrene units). Proteins are polymers of amino acids (hence the term polypeptide), and nucleic acids are polymers of nucleotides. But fluorescein is a small molecule (MW 332.31Da) and is not made up of subunits. For these reasons, fluorescein is not a polymer according to the ordinary and accustomed meaning of the term, and would <u>not</u> be understood by a person of ordinary skill in the art to be a polymer.

[0004] Throughout my career I have never heard the term "polymer" applied to fluorescein or to any related molecule. I understand the Examiner has taken the position that fluorescein is a polymer of –CH- units. However, this use of the term would not be understood by scientists of ordinary skill in this technical field because –CH is not considered a subunit because this definition is far too broad. Taking this meaning of a subunit, virtually any organic molecule would qualify as a polymer and the term "polymer" would lose its usefulness as a descriptive term, and therefore the term would become meaningless. Rather, persons of ordinary skill in the art ordinarily understand a "polymer" to be a large molecule consisting of repeating sub-units, such as those mentioned above as examples, and do not consider fluorescein to be a polymer. As a

small molecule, fluorescein also is not considered and would not be understood by persons of ordinary skill in the relevant field as a "macromolecule," according to the ordinary and accustomed meaning of that term.

[0005] According to its ordinary and accustomed meaning, the term "carrier macromolecule" refers to a large (sometimes polymeric) molecule that acts to carry another molecule in an assay. Usually the carried molecule is covalently attached to the carrier. Examples of macromolecules that are commonly used as carrier macromolecules are certain large proteins (e.g., bovine albumin [MW 68,000Da] and keyhole limpet hemocyanin [MW ~10,000,000Da]), polymers (e.g. polystyrene), and metal colloids (e.g. colloidal gold). These are the types of molecular structures that are referred to by the term "carrier macromolecule," in contexts where these macromolecules are used to carry another molecule into or through an assay. I point out that the specification (at paragraphs 14 and 15) provides examples of macromolecules that can act as carrier macromolecules.

[0006] I am informed that the Examiner has taken the position in this patent prosecution that fluorescein is a macromolecule. But according to its ordinary meaning in the relevant field, flourescein would not be considered a macromolecule because it is simply too small. Macromolecules have molecular weights in the thousands, and certainly not a mere 332 like fluorescein. Therefore, the ordinary meaning of the term "macromolecule" in the relevant field would certainly not encompass fluorescein.

[0007] I am also informed the Examiner has taken the position in this patent prosecution that a sheet of nitrocellulose used in a nucleic acid binding assay would be considered as a "carrier macromolecule" by a person of ordinary skill. This is an incorrect meaning of "carrier macromolecule." Nucleic acid procedures typically have a solid phase and a mobile phase. The term "carrier" indicates that this component of the assay is moving. Nitrocellulose is often used in assays as the (non-moving) solid-phase support. I have never heard of a solid phase (including a nitrocellulose membrane) being referred to as a "carrier macromolecule" in my scientific career. For these reasons it is my opinion that the ordinary and accustomed meaning of a "carrier macromolecule" in

the relevant art does not encompass a nitrocellulose sheet being used as a solid phase in a nucleic acid assay.

Closing

[0008] I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Samuel A. Lewis, Ph.D.

17 Mar 06
Date

APPENDIX A

1) Grubman M.J., Lewis S.A., and Morgan D.O., 1993. Protection of swine against foot-and-mouth disease with viral capsid proteins expressed in heterologous systems. *Vaccine*, 11:825-829.

2) Lewis S.A., Morgan D.O., and Grubman, M.J., 1991. Expression, processing, and assembly of foot and mouth disease virus capsid structures in heterologous systems: induction of a neutralizing antibody response in guinea pigs. *J. Virol.*, 65:6572-6580.

3) Grubman, M.J and Lewis S.A., 1992. Identification and characterization of the structural and nonstructural proteins of african horsesickness virus and determination of the genome coding assignments. *Virol.*, 186:444-451.

4) Lewis, S.A. and Grubman, M.J., 1991. VP2 is major exposed protein on orbiviruses. *Arch. Virol.* 121:233-236.

5) Lewis, S.A. and Grubman, M.J., 1990. Bluetongue virus-17: Surface exposure of VP7. *Virus Res.*, 16:17-26.

6) Lewis, S.A., and Strand, M., 1991. Characterization of proteins and immunogens released by adult *Schistosoma mansoni*. *J. Parasitol.* 77(2):263-271.

7) Dalton, J.P., Lewis, S.A., Aronstein, W.S., and Stand, M., 1987. *Schistosoma mansoni*: Immunogenic glycoproteins of the cercarial glycocalyx. *Exp. Parasitol.*, 63:215-226.

8) Aronstein, W.S., Lewis, S.A., Norden, A.P., Dalton, J.P., and Strand, M., 1986. Molecular identity of a major antigen of *Schistosoma mansoni* which cross-reacts with *Trichinella spiralis* and *Fasciola hepatica*. *Parasitol.*, 92:133-151.